REMARKS

Claims 48-56, 58-65 and 67-69 are pending in the present application. Claims 48, 60, 63-65 and 67-69 have been amended. New Claims 86-96 have been added. These new laims do not add any new matter.

Claims 1-47, 57, 66 and 70-85 have been withdrawn in response to a restriction requirement. Applicants retain the right to pursue these claims in a separate divisional application.

Objection to the Specification

The Examiner has objected to the Specification for the lack of SEQ ID NOS. where required pursuant to 37 CFR 1.821, for the omission of an ATCC Deposit No. on page 46, line 17 and for the improper designation of trademarks.

Applicants have amended the Specification to address these objections and believe they have all been corrected.

Objection to the Claims

Claim 63 was objected to for not including the ATCC No. for the hybridoma cell line designated 94A7 (see Specification, line 16). Claim 63 has been amended to include the ATCC number.

Claims 67-69 were objected to for dependence on a non-elected claim and have been amended to remove this dependency.

Applicants believe that with the amendments to Claims 63, and 67-69, all objections have been removed.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 63 and 67 under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim 63 was considered indefinite for omission of an identifying ATCC No. As indicated above, this claim has been amended to include the appropriate ATCC No.

Claim 67 was considered indefinite for use of improper Markush group language. This claim has been amended to correct the language.

Applicants believe that the amendments to Claims 63 and 67 address the Examiner's concerns and and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected Claims 61 and 67 under 35 U.S.C. 112, first paragraph, as not enabling one skilled in the art to use the invention.

The basis of this rejection is (a) the inability of the Examiner to locate a deposit identified by "PTA-4561" (hybridoma 14C7) at the ATCC web-site and (b) the fact that the hybridoma 94A7, although presumably deposited, has no identifying ATCC No. and could also not be found within the ATCC database.

Applicants have amended both the Specification and Claim 67 to include the ATCC designation of PTA-5553, to refer to the deposited hybridoma 94A7. Applicants have also amended the Specification to change the description of this ATCC identifier from "accession number" to "Patent Deposit Designation".

Applicants' contacted the ATCC and were informed that deposits submitted for and referenced in a pending patent application are not included in the ATCC searchable product directory, as they are not made available to the public until granting of the patent.

Applicants have enclosed herewith copies of the ATCC receipts for both hybridomas 14C7 and 94A7, (PTA-4561 and PTA-5553, respectively), as evidence of the fact that both hybridomas have, in fact, been deposited with the ATCC.

Applicants believe that with the amendment to Claim 67 and submission of copies of the ATCC receipts, the Examiner's concern hs been addressed and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §102(e)

The Examiner has rejected Claims 48-56, 58-61, 63-65 and 67-69 under 35 U.S.C. 102(e) as being anticipated by Mu et al.

Mu et al. disclose an antibody to the hepsin protein. To be rejected under 35 U.S.C. 102(e), the anticipating reference must include every element of the claim under consideration (*W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, at 313 (Fed. Cir. 1983). There must be no difference between the claimed invention and the reference disclosure (*Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, at 1010 (Fed. Cir. 1991).

Claim 48 has been amended to indicate that the antibodies are raised against a modified hepsin molecule consisting of SEQ ID NO:9.

As Mu et al. do not disclose generation of antibodies directed against SEQ ID NO:9, Applicants believe that the rejection of Claims 48-56, 58-61, 63-65 and 67-69 under 34 U.S.C. 102(e) has been overcome and respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §102(e)

The Examiner has rejected Claims 48-56, 58-61, 63-65 and 67-69 under 35 U.S.C. 102(e) as being anticipated by O'Brien et al.

O'Brien et al. disclose an antibody to the hepsin protein. To be rejected under 35 U.S.C. 102(e), the anticipating reference must include every element of the claim under consideration (*W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, at 313 (Fed. Cir. 1983). There must be no difference between the claimed invention and the reference disclosure (*Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, at 1010 (Fed. Cir. 1991).

Claim 48 has been amended to indicate that the antibodies are raised against a modified hepsin molecule consisting of SEQ ID NO:9.

As O'Brien et al. do not disclose generation of antibodies directed against SEQ ID NO:9, Applicants believe that the rejection of Claims 48-56, 58-61, 63-65 and 67-69

under 34 U.S.C. 102(e) has been overcome and respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §103 (a)

The Examiner has rejected Claims 48-56, 58-61, 63-65 and 67-69 under 35 U.S.C. §103 (a) as being unpatentable over Mu et al. in view of Hellstrom et al.

The Examiner states that Mu et al. discloses an antibody to hepsin protein or polypeptide portions thereof, including monoclonal, polyclonal, single-chain and engineered antibodies, as covered primarily in paragraphs [0021], [0121], [0169], [0172] and [0175]. Within these paragraphs, Mu et al. reference methodology known to one of skill in the art regarding the generation of such antibodies. However, Mu et al. only disclose preparation of one polyclonal antibody to hepsin, generated using a 19-mer C-terminal peptide (see paragraph [0246]).

Applicants presume that the Examiner has concluded that generation of antibodies to intact hepsin, given the knowledge of the protein sequence, would be considered obvious to one of "skill in the art".

However, contrary to the Examiner's conclusion, the generation of antibodies to hepsin, in practical terms, has not proved to be straightforward. Attempts by Applicants to generate monoclonal antibodies to the hepsin molecule using conventional methods were not successful. A search by Applicants of PubMed using the terms "antibodies and hepsin" turns up only five publications. One reference, which comes from the laboratory of the Applicants, describes production of antibodies raised to and directed against an intact hepsin molecule. The other publications all refer back to one series of polyclonal antibodies raised to a series of peptide fragments of the hepsin molecule (see Kurachi et al. (1994) Methods in Enz., Vol 244, cited in the Supp. IDS submitted on Feb 10, 2005)) that not proved to be very effective.

In the instant application, Applicants addressed the problems in production of antibodies to intact hepsin. Applicants believed that these problems resulted from the fact that (a) hepsin is found in all mammals and (b) the sequences of mouse and human hepsin are almost the same. Because of this facts, Applicants concluded that human

hepsin does not act as an adequate immunogen in mice. Applicants overcame this problem, as described in the Specification (Page 46, Lines 29-31) by "immunizing a hepsin knock-out animal, e.g. a hepsin knock out-mouse (U.S. Patent No. 5,981,830)". Such a mouse does not contain a hepsin gene and would therefore provide the necessary immunological background to allow human hepsin to act as an immunogen, resulting in generation of antibodies directed against a human hepsin molecule. Mu et al. do not disclose the use of anything other than previously published methods for generation of monoclonal antibodies to hepsin and they do not actually generate any monoclonal antibodies.

Furthermore, the isolation by the Applicants of the modified hepsin molecule, i.e. Hepsin-ED-EK (SEQ ID NO:9), allowed Applicants to generate large amounts of a purified hepsin immunogen (See Specification, Pages 84-85). Mu et al. do not disclose such a modified hepsin molecule.

Applicants maintain that it is only the use of "hepsin knock-out" mice, which are hepsin-deficient, in conjunction with the use of the modified hepsin molecule (SEQ ID NO:9) disclosed in the instant application that allowed the Applicants to successfully generate the anti-hepsin monoclonal antibodies claimed in the instant application.

In light of the arguments presented above, Applicants respectfully request that the rejection of Claims 48-56, 58-61, 63-65 and 67-69 under 35 U.S.C. §103 (a) be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for early examination and action toward that end is respectfully requested.

The Commissioner is hereby authorized to charge deposit account 02-2117 for any fees necessary including the three-month extension of time. This is not, however, authorization to charge the issue fee. Two copies of this paper are enclosed for this purpose.

Respectfully submitted,

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